VII. Management of Specific Dyslipidemias

Randomized clinical trials generally have not focused on specific dyslipidemias. Yet these disorders are common enough to deserve specific attention in ATP III. In this section, the major dyslipidemias will be reviewed. Recommendations for their management are derived from the considered judgment of the ATP III panel. Recommendations are based in part on the sizable body of literature that describes changes in serum lipid and lipoprotein levels produced by dietary and drug therapies. In some dyslipidemias, combined drug therapy is required to obtain optimal lipoprotein profiles. In general, improvements in lipoprotein profiles rather than favorable clinical outcomes are the end points that serve as the basis for recommendations. These recommendations are made with the recognition that some induced changes in the lipoprotein profile have not been proven through clinical trial to reduce risk for CHD. Instead, they generally represent a synthesis of several lines of indirect evidence.

1. Very high LDL cholesterol

Severe forms of elevated LDL cholesterol are defined as those in which LDL concentrations are persistently $\geq$190 mg/dL after TLC. Most elevations of this degree have a strong genetic component. Table VII.1–1 identifies three familial forms of elevated LDL cholesterol, i.e., familial hypercholesterolemia (heterozygous and homozygous forms), familial defective apolipoprotein B-100, and polygenic hypercholesterolemia. Clinical features, clinical outcomes, and therapeutic considerations are listed in the table and are discussed in more detail below.

Table VII.1–1. Familial Disorders That Cause Very High LDL-Cholesterol Levels (≥190 mg/dL)

Clinical Condition	Clinical Features and Clinical Outcomes	Therapeutic Considerations
Heterozygous familial hypercholesterolemia (FH)	• Due to mutated LDL receptor (half normal-expression) • Prevalence: 1/500 in United States • LDL-C levels: twice normal (e.g., 190–350 mg/dL) • Tendon xanthomas common • Premature CHD common – 30–40's in men – 40–50's in women	• Begin LDL-lowering drugs in young adulthood • TLC: all persons • Statins: first line of therapy (start dietary therapy simultaneously) • BAS* (if necessary in combination with statins) • If needed, consider triple-drug therapy (statins + BAS + nicotinic acid)
Homozygous familial hypercholesterolemia (FH)	• Due to two mutated LDL receptors • Prevalence: 1/1,000,000 in United States • LDL-C levels: 4-fold increase (e.g., 400–1000 mg/dL) • Xanthomas: tendinous, tuberous, dermal • Widespread, severe athero-sclerosis (multiple arterial beds affected) • Very severe clinical athero-sclerotic disease • Aortic valve disease	• Dietary therapy not effective • BAS not effective • Nicotinic acid mildly effective • Statins may be moderately effective in some persons • Ileal exclusion operation not effective • Liver transplant effective, but impractical • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia)
Familial defective apolipoprotein B-100 (FDB)	• Due to mutated apo B-100 (position 3500 A→G) • Prevalence 1/700–1000 • LDL-C levels: 1.5–2-fold increase (e.g., 160–300 mg/dL) • Xanthomas: tendon • Premature CHD – CHD 40–65yr common in men – Uncertain in women	• TLC indicated • All LDL-lowering drugs are effective • Combined drug therapy required less often than in heterozygous FH
Polygenic hypercholesterolemia	• Due to multiple gene polymorphisms (often combined with dietary excesses) • Prevalence: 1/10–20 (depending on age) • LDL-C: ≥190 mg/dL • Prevalence of CHD: 3–4-fold increase (above average)	• TLC indicated (all persons) • Consider for drug therapy (if LDL-C ≥190 mg/dL after dietary therapy [all persons]) • All LDL-lowering drugs are effective • If necessary to reach LDL-C goals, consider combined drug therapy

* BAS=bile acid sequestrants.

a. Familial hypercholesterolemia (FH)

Heterozygous familial hypercholesterolemia. This autosomal-dominant disorder occurs in 1 of every 500 people (Goldstein and Brown, 1995). The defect is a mutation in the gene for the LDL receptor (Brown and Goldstein, 1986); a large number of mutations affecting LDL receptor function has been reported (Hobbs et al., 1990; Hobbs et al., 1992). In all of these, half the normal number of receptors are expressed. Hypercholesterolemia often is detectable at birth or shortly thereafter, and total cholesterol levels eventually rise to 350 to 500 mg/dL in many persons. Tendon xanthomas, especially in the Achilles tendons and the extensor tendons of the hands, are typical. FH carries increased risk of premature CHD; CHD commonly occurs in men by the fourth or fifth decade, and about 10 years later in women. Treatment for FH heterozygotes should begin with TLC, but drug therapy is generally required as well. For adults with heterozygous FH, LDL-lowering drugs should be initiated as soon as it is recognized that the LDL-cholesterol goal cannot be achieved with TLC alone. Persons with milder forms of heterozygous FH may respond sufficiently to therapy with a bile acid sequestrant or a statin. More severe cases require two-drug therapy (e.g., statin plus bile acid sequestrant) (Mabuchi et al., 1983; Bilheimer et al., 1983) or even triple-drug therapy (statin plus bile acid sequestrant plus nicotinic acid) (Malloy et al., 1987; Kane et al., 1990). Because of the high risk of premature CHD accompanying heterozygous FH, drug therapy is cost effective.

Homozygous familial hypercholesterolemia occurs in only 1 in 1 million persons (Goldstein and Brown, 1995). LDL-receptor activity is essentially absent, and total cholesterol levels commonly run between 700 and 1,200 mg/dL. Cutaneous xanthomas form at various sites within the first few months or years of life, whereas tendon and tuberous xanthomas develop later. Atherosclerosis is severe and widespread, affecting coronary, carotid, iliac, and femoral arteries, and the aortic root. Treating FH homozygotes is difficult because the persons express little or no LDL-receptor activity and therefore are resistant to the effects of therapeutic diets and most cholesterol-lowering medications. High doses of statins may produce some cholesterol reduction in a few FH homozygotes, as does nicotinic acid. In the past, various surgical procedures have been tested. Ileal bypass surgery is not effective. Portacaval shunt surgery only modestly lowers LDL levels (Starzl et al., 1978; Bilheimer et al., 1975; Bilheimer 1989). Liver transplantation provides new LDL receptors that dramatically reduce LDL-cholesterol levels (Bilheimer 1989); further, responsiveness to LDL-lowering drugs returns. However transplantation requires continuous immunosuppression and is not a practical approach. Current accepted therapy consists of modified forms of plasmapheresis that selectively remove VLDL and LDL from the plasma. Early studies laid the foundation for this approach (Thompson and Myant, 1980; King et al., 1980; Eisenhauer et al., 1986; Homma et al., 1986; Mabuchi et al., 1986). The FDA has more recently approved commercial techniques for this purpose: (a) heparin-induced extracorporeal lipoprotein precipitation, and (b) a dextran sulfate cellulose absorbent. Such treatment must be performed every 1 to 3 weeks, depending on the clinical state of the patient, in order to promote xanthoma regression and retard atheroma formation.

b. Familial defective apolipoprotein B-100 (FDB)

FDB is an autosomal dominant abnormality that causes elevated LDL cholesterol (Vega and Grundy, 1986; Soria et al., 1989; Innerarity et al., 1987; Innerarity et al., 1990). It results from a

single nucleotide mutation that substitutes glutamine for arginine at amino acid position 3,500 in apolipoprotein B. This mutation reduces affinity of LDL particles for the LDL receptor; consequently, the LDL of affected individuals is cleared from plasma more slowly than normal. FDB prevalence varies among different populations. In the United States it occurs in about 1 in 700–1000 people (Innerarity et al., 1990). Serum LDL levels are often similar to those described for persons with heterozygous FH. Affected individuals can manifest premature atherosclerosis and tendon xanthomas. However, other affected individuals have a more moderate form of hypercholesterolemia, indistinguishable from polygenic hypercholesterolemia (see below). The diagnosis requires molecular screening techniques available only in specialized laboratories. Treatment is similar to that of heterozygous FH; however, less intensive intervention may achieve the goals of therapy (Raal et al., 1997).

c. Polygenic hypercholesterolemia

LDL-cholesterol levels ≥190 mg/dL characterize polygenic hypercholesterolemia. No unique genetic defect is responsible; rather the high LDL-cholesterol level is explained by a complex interaction of environmental and genetic factors. A variety of patterns of LDL metabolism have been reported (Vega et al., 1991). The disorder is associated with increased risk for premature CHD. In polygenic hypercholesterolemia, the elevation in plasma cholesterol is generally milder than in heterozygous FH, and tendon xanthomas are not observed. Only about 7 percent of the first-degree relatives of persons with polygenic hypercholesterolemia have high LDL-cholesterol levels. Treatment of polygenic hypercholesterolemia is essentially identical to that given for heterozygous FH, although drugs in combination are required in fewer cases.

2. Elevated triglycerides

a. Classification, causation, and clinical significance

1) Classification of serum triglycerides

Because of the growing evidence for a strong association between elevated triglycerides and CHD risk, ATP III adopts lower cutpoints for triglyceride abnormalities than did ATP II (National Cholesterol Education Program 1993; 1994) (see Section II.3).

Category	Serum Triglyceride Levels (mg/dL)
Normal triglycerides	Less than 150
Borderline high triglycerides	150 to 199
High triglycerides	200 to 499
Very high triglycerides	≥500

Terminology for triglyceride levels is similar to that used for LDL cholesterol. Borderline high triglycerides (150–199 mg/dL) are a common component of the metabolic syndrome. The same is true for high triglycerides (200–499 mg/dL) except that genetic factors play a more important role. Very high triglycerides (≥500 mg/dL) also have a strong genetic component and are

accompanied by increasing risk for acute pancreatitis. High triglycerides equate to the older definition of type 4 hyperlipoproteinemia, whereas very high triglycerides were called type 5 hyperlipoproteinemia (Fredrickson et al., 1967a-e).

2) Causes of elevated triglycerides

The causes of raised serum levels of triglycerides in each category of elevated triglyceride are listed in Table VII.2–1.

Table VII.2–1. Classification and Causes of Elevated Serum Triglycerides

Classification of Serum Triglycerides	Causes of Elevated Serum Triglycerides
Normal triglycerides (<150 mg/dL)	
Borderline High Triglycerides (150–199 mg/dL)	• Acquired causes – Overweight and obesity – Physical inactivity – Cigarette smoking – Excess alcohol intake – High carbohydrate intake (>60% of total energy) • Secondary causes* • Genetic causes – Various genetic polymorphism
High Triglycerides (200–499 mg/dL)	• Acquired causes – Same as for borderline high triglycerides (usually combined with foregoing causes) • Secondary causes* • Genetic patterns – Familial combined hyperlipidemia – Familial hypertriglyceridemia – Polygenic hypertriglyceridemia – Familial dysbetalipoproteinemia
Very High Triglycerides (≥500 mg/dL)	• Usually combined causes – Same as for high triglycerides • Familial lipoprotein lipase deficiency • Familial apolipoprotein CII deficiency

* Secondary causes of elevated triglycerides: diabetes mellitus (see Diabetic Dyslipidemia), chronic renal failure, nephrotic syndrome, Cushing's disease, lipodystrophy, pregnancy, and various drugs (corticosteroids, beta-blockers, retinoids, oral estrogens [not transcutaneous estrogen], tomoxifen, protease inhibitors for AIDS).

Borderline high triglycerides (150–199 mg/dL). In most persons, borderline high triglycerides derive from acquired factors (Table VII.2–1). Acquired factors include overweight and obesity,

physical inactivity, excess alcohol intake, and in some persons, high-carbohydrate diets. Genetic factors play a lesser role (Heller et al., 1993; Boomsma et al., 1996). It is also important to rule out secondary causes (see footnote Table VII.2–1).

High Triglycerides (200–499 mg/dL). Generally, genetic and acquired factors combine to produce high serum triglycerides. Many persons with high triglycerides manifest insulin resistance and the metabolic syndrome. Abdominal obesity is especially common among those with high triglycerides (Bodkin et al., 1993; Julien et al., 1997). With high triglycerides, genetic factors play an increasingly predominant role (Assmann and Brewer, 1991; Humphries et al., 1994; Galton 1995). Patterns of dyslipidemia have been found to cluster in some families, suggesting a strong genetic component. Three patterns for family clustering of elevated triglycerides have been identified; they are called *familial combined hyperlipidemia, familial hypertriglyceridemia,* and *familial dysbetalipoproteinemia.* Each pattern is reviewed briefly.

In *familial combined hyperlipidemia*, affected persons and their first-degree relatives may at various times manifest high serum cholesterol, high triglycerides, or both (Goldstein et al., 1973a,b; Hazzard et al., 1973). Whether the underlying defect is monogenic or polygenic is not known. Metabolic studies suggest that the liver overproduces VLDL, but other metabolic defects may be present (Chait et al., 1980; Beil et al., 1982b; Venkatesan et al., 1993). Many persons exhibit high levels of apo B-100 (hyperapobetalipoproteinemia) (Teng et al., 1986; Kwiterovich et al., 1987; Austin et al., 1992). There are no specific clinical features to diagnose this disorder. When total cholesterol is high, the level is typically in the range of 250 to 350 mg/dL. Triglyceride levels vary considerably, but about two-thirds of the persons have levels in the range of 200 to 500 mg/dL. Hyperlipidemia may or may not be present in childhood. Familial combined hyperlipidemia is associated with increased risk for premature CHD. In an early study, about 10 percent of persons with early onset myocardial infarction fell in the category of this disorder (Goldstein et al., 1973a,b; Hazzard et al., 1973).

Family clustering of elevated triglycerides without increased serum cholesterol levels characterizes *familial hypertriglyceridemia* (Goldstein et al., 1973a,b; Hazzard et al., 1973). Persons with familial hypertriglyceridemia seemingly do not carry as high a risk for premature CHD as do those with familial combined hyperlipidemia (Brunzell et al., 1976; Austin et al., 2000). This is not surprising because the former generally have lower levels of LDL cholesterol than the latter. Many persons with familial hypertriglyceridemia also manifest obesity (Dunn et al., 1985), but in some, triglycerides are elevated without obesity or any other evidence of the metabolic syndrome. These latter persons may have a defect in catabolism of TGRLP (e.g., an abnormality in lipoprotein lipase activity) (Wilson et al., 1990; Minnich et al., 1995).

A third category of familial clustering of elevated triglycerides includes those with increased remnant lipoproteins (*familial dysbetalipoproteinemia)* (Mahley and Rall, 1995). This condition also has been named type 3 hyperlipoproteinemia (Fredrickson et al., 1967a-e). The defining defect in this disorder is an isoform variation in apolipoprotein E. Among the three major isoforms, E2, E3, and E4, the one most often associated with dysbetalipoproteinemia is apo E2. Affected persons usually are homozygous for apo E-2. Since apo E mediates binding of VLDL remnants and chylomicron remnants to their hepatic receptors, these remnants accumulate in plasma when the dysfunctional apo E-2 is present. The frequency of apo E-2 homozygosity in

the general population is approximately 1 in 100, but the clinical syndrome of dysbetalipoproteinemia occurs much less frequently. The difference in frequency between the permissive genotype and the clinical syndrome is explained by the requirement for other factors, including age, hypothyroidism, obesity, diabetes mellitus, or the coincident presence of another genetic lipoprotein disorder, such as familial combined hyperlipidemia, to fully express the syndrome. Some persons have palmar xanthomas of the creases of the palms and fingers, but these may progress to nodules several millimeters in size. Tuberoeruptive xanthomas occur and vary from small papules to larger lesions. Premature atherosclerotic disease may present as myocardial infarction, stroke, or peripheral arterial disease. Hyperlipidemia is accentuated by concomitant glucose intolerance, diabetes mellitus, hyperuricemia, hypothyroidism, and obesity. The disorder is not commonly expressed in childhood.

Very high triglycerides (≥500 mg/dL). When serum triglycerides exceed 500 mg/dL, chylomicrons usually begin to appear in fasting plasma. Their presence typically denotes a catabolic defect for TGRLP (Kesaniemi and Grundy, 1984). Most frequently reported are genetic defects in lipoprotein lipase or apo CII. (Santamarina-Fojo 1998). Impaired catabolism of TGRLP also is induced by overproduction of apo CIII, an inhibitor of lipoprotein lipase activity (Aalto-Setala et al., 1996; Ebara et al., 1997; Batal et al., 2000). Excessive production of apo CIII can be a consequence of the insulin-resistance state (Li et al., 1995). Many persons with very high triglycerides have both overproduction and defective catabolism of TGRLP (Kesaniemi and Grundy, 1984). Sometimes very high triglycerides are found in families with familial combined hyperlipidemia or familial hypertriglyceridemia. Although some persons with very high triglycerides remain free from CHD throughout their lives, others develop premature CHD (Steiner et al., 1971; Greenberg et al., 1977). The latter may be due in part to the presence of atherogenic TGRLP, but the metabolic syndrome also is common in these persons. When triglycerides exceed 1000 mg/dL, persons are at risk for acute pancreatitis (Chait and Brunzell, 1992). Because of the danger of acute pancreatitis, persons with severely elevated triglycerides (>2000 mg/dL) should be treated as a medical urgency.

3) Relation of elevated triglycerides to CHD and other conditions

As shown in Table VII.2–2, triglycerides are related to CHD in several ways.

Table VII.2–2. Relationship of Elevated Triglycerides to CHD and Other Conditions

Classification of Serum Triglycerides	Clinical Significance
Normal triglycerides (<150 mg/dL)	
Borderline High Triglycerides (150–199 mg/dL)	• Marker for atherogenic dyslipidemia – Elevated small LDL particles – Low HDL cholesterol • Marker for the metabolic syndrome – Elevated blood pressure – Insulin resistance and glucose intolerance – Prothrombotic state – Proinflammatory state
High Triglycerides (200–499 mg/dL)	• Elevated atherogenic remnant lipoproteins • Marker for other components of atherogenic dyslipidemia (see above) • Marker for the metabolic syndrome (see above)
Very High Triglycerides (≥500 mg/dL)	• Metabolic syndrome, type 2 diabetes, and increased risk for CHD common • Increased risk for acute pancreatitis (risk proportional to triglyceride elevation above 1000 mg/dL) • Chylomicronemia syndrome (triglycerides >2000 mg/dL) – Eruptive skin xanthomas – Hepatic steatosis – Lipemia retinalis – Mental changes – High risk for pancreatitis

Borderline high triglycerides (150–199 mg/dL) are primarily a marker for other atherogenic factors—small LDL particles, low HDL cholesterol, and other components of the metabolic syndrome. High triglycerides (200–499 mg/dL) reflect the presence of atherogenic remnant lipoproteins as well as being a marker for atherogenic dyslipidemia and the metabolic syndrome. When remnants are enriched with cholesterol ester (dysbetalipoproteinemia), CHD risk is particularly high. Finally, some persons with very high triglycerides (≥500 mg/dL) carry other atherogenic factors—increased remnant lipoproteins, atherogenic dyslipidemia and the metabolic syndrome—and hence are at increased risk for CHD. However a more urgent concern in such persons is an increased risk of acute pancreatitis (Chait and Brunzell, 1992). This risk increases in proportion to the rise in triglyceride levels. When triglycerides exceed 2000 mg/dL, persons are subject to the chylomicronemia syndrome (Chait and Brunzell, 1992), which is characterized by eruptive skin xanthomas, lipemia retinalis, mental changes and acute pancreatitis. If very high triglycerides are due exclusively to a catabolic defect of serum triglycerides (e.g., deficiencies of lipoprotein lipase or apo CII), the patient may not be at increased risk for CHD.

b. Therapeutic considerations for persons with elevated triglycerides

1) Non-HDL cholesterol: secondary target for persons with elevated triglycerides

Persons with elevated triglycerides typically have an associated increase in atherogenic VLDL remnants. Higher serum levels of VLDL cholesterol reflect this increase. Since VLDL remnants appear to have atherogenic potential similar to that of LDL, VLDL cholesterol can be added to LDL cholesterol to become a secondary target of therapy. VLDL + LDL cholesterol, termed non-HDL cholesterol, equals total cholesterol minus HDL cholesterol. Relations among the different lipoprotein fractions are as follows:

1) Total cholesterol = LDL + VLDL + HDL

2) Total cholesterol – HDL = LDL + VLDL = non-HDL

A normal VLDL cholesterol can be considered to be a level <30 mg/dL (Heiss et al., 1980). Thus, a therapeutic goal for non-HDL cholesterol can be 30 mg/dL higher than the goal for LDL cholesterol (Table VII.2–3). For persons with borderline high triglycerides (150–199 mg/dL), the VLDL cholesterol is not elevated enough to evoke non-HDL cholesterol as a secondary target. However, non-HDL cholesterol becomes an appropriate secondary target when triglycerides are in the range of 200–499 mg/dL. When triglycerides are very high (≥500 mg/dL), some of the cholesterol in TGRLP may be present in nonatherogenic lipoproteins, e.g., large VLDL and chylomicrons. Moreover, current triglyceride-lowering therapies may not be sufficient to attain non-HDL-cholesterol goals for persons with very high triglycerides. Rather than risk possible side effects of combined therapy with lipid-lowering drugs it may be preferable to allow the non-HDL-cholesterol level to remain above the recommended goal.

Table VII. 2–3. Non-HDL-Cholesterol Goal Corresponding to LDL-Cholesterol Goals

LDL-Cholesterol Goal	Non-HDL-Cholesterol Goal
<160 mg/dL	<190 mg/dL
<130 mg/dL	<160 mg/dL
<100 mg/dL	<130 mg/dL

2) Changes in life habits are primary therapy for elevated triglycerides

Elevated serum triglycerides in the general population are due principally to acquired life habits including overweight and obesity, physical inactivity, excess alcohol intake, cigarette smoking, and in some persons, high-carbohydrate diets. The goal of therapy is to reduce atherogenic VLDL remnants and to mitigate the associated lipid and nonlipid risk factors of the metabolic syndrome. The following changes in life habits are the foundation of therapy for elevated triglycerides:

- Body weight control
- Regular physical activity

- Smoking cessation
- Restriction of alcohol use (in selected persons)
- Avoidance of high-carbohydrate diets

Recommendations for the institution of each of these life-habit changes are discussed in Section V.

3) Special treatment considerations for different triglyceride categories (Table VII.2–4)

Table VII.2–4. Treatment Considerations for Elevated Serum Triglycerides

Serum Triglyceride Category	Special Treatment Considerations
Borderline High Triglycerides (150–199 mg/dL)	• Primary goal: achieve LDL-C goals • Life-habit changes: first-line therapy for borderline high triglycerides – Body weight control – Regular physical activity – Smoking cessation – Restriction of alcohol use (when consumed in excess) – Avoid high carbohydrate intakes (>60% of calories) • Drug therapy: – Triglycerides in this range not a direct target of drug therapy
High Triglycerides (200–500 mg/dL)	• Primary goal: achieve LDL-C goals • Secondary goal: achieve non-HDL-C goal: 30 mg/dL higher than LDL-C goal • First-line therapy for high triglycerides: TLC-emphasize weight reduction and increased physical activity • Second-line therapy: drugs to achieve non-HDL-C goals – Statins: lower both LDL-C and VLDL-C – Fibrates: lower VLDL-triglycerides and VLDL-C – Nicotinic acid: lower VLDL-triglycerides and VLDL-C • Alternate approaches to drug therapy for lowering non-HDL-C – High doses of statins (lowers both LDL-C and HDL-C) – Moderate doses of statins and triglyceride-lowering drug (fibrate or nicotinic acid): **Caution**: increased frequency of myopathy with statins + fibrates
Very High Triglycerides (≥500 mg/dL)	Goals of therapy: • Triglyceride lowering to prevent acute pancreatitis (first priority) • Prevention of CHD (second priority) Triglyceride lowering to prevent pancreatitis: • Very low-fat diet when TG >1000 mg/dL (<15% of total calories as fat) • Medium chain triglycerides when TG >1000 mg/dL (can replace long chain triglycerides in diet) • Institute weight reduction/physical activity • Fish oils (replace some long-chain triglycerides in diet) • Triglyceride-lowering drugs (fibrate or nicotinic acid): most effective • Statins: not first-line agent for very high triglycerides (statins not powerful triglyceride-lowering drugs) • Bile acid sequestrants: contraindicated—tend to raise triglycerides Triglyceride lowering to prevent CHD: • Efficacy of drug therapy to prevent CHD in persons with very high triglycerides not demonstrated by clinical trials

Borderline high triglycerides (150–199 mg/dL). Serum triglycerides in the range of 150–199 mg/dL often indicate adverse life habits, as noted in the previous section. Borderline high triglycerides should alert the physician to the presence of the metabolic syndrome and should signal the need for changes in life habits. When triglycerides are borderline high, LDL cholesterol remains the primary target of treatment and it is not necessary to evoke non-HDL cholesterol as a secondary target of therapy. Drug therapy to specifically reduce VLDL remnants is rarely needed for triglycerides in this range, although statins concomitantly lower LDL and VLDL remnants. Thus the general approach to management of elevated LDL cholesterol need not be modified when triglycerides are borderline high. Nonetheless, some persons with borderline high triglycerides have low HDL cholesterol, which may influence the choice of drugs as described in the previous section. Even so, when drug therapy is needed, LDL-lowering drugs generally take priority. In the presence of low HDL cholesterol, nicotinic acid represents an alternative therapy provided the goals for LDL cholesterol are achieved. Further, as previously noted, fibrate therapy is another option for persons with low HDL cholesterol, low LDL cholesterol, and borderline high triglycerides. The positive outcome with gemfibrozil therapy in the VA-HIT trial in persons with this profile places fibrates on the list of alternatives (Rubins et al., 1999).

High triglycerides (200–499 mg/dL). In persons with high serum triglycerides, LDL cholesterol remains the primary target of therapy. In addition, non-HDL cholesterol becomes a secondary target. Changes in life habits, as outlined before, represent first-line therapy, but it is also important to determine whether a patient is taking drugs known to exacerbate hypertriglyceridemia, and, if so, these should be modified. Among hypolipidemic agents, the statins are the most effective for lowering non-HDL cholesterol. Not only do statins reduce LDL cholesterol, but they also lower VLDL triglycerides and VLDL cholesterol (Stein et al., 1998). For example, in persons with triglyceride levels between 200 and 499 mg/dL, the statins lower triglycerides by 20–40 percent, and VLDL cholesterol is lowered to a similar degree as LDL cholesterol (Vega and Grundy, 1990b). On the other hand, the presence of hypertriglyceridemia of any magnitude is a relative contraindication to bile acid sequestrants when used as monotherapy since these drugs usually promote an increase in triglyceride levels (Crouse 1987).

When LDL-cholesterol levels are not significantly elevated, the goal for non-HDL cholesterol with a triglyceride-lowering drug usually is within reach. Among these, nicotinic acid is usually the most effective; it reduces triglycerides by 30–50 percent usually without causing a reciprocal increase in LDL concentrations (Martin-Jadraque et al., 1996). At the same time, nicotinic acid therapy commonly raises HDL-cholesterol concentrations by 20–30 percent. In persons with contraindications to nicotinic acid or in whom this drug is poorly tolerated, fibric acid derivatives (gemfibrozil 600 mg twice daily, fenofibrate 200 mg once daily) reduce triglycerides by 40–60 percent, and cause a 15–25 percent increase in HDL-cholesterol concentrations. Nevertheless, fibrates often raise LDL-cholesterol levels by 5–30 percent (by forming larger LDL particles). This reciprocal increase in LDL cholesterol usually means that fibrates alone do not lower non-HDL-cholesterol levels (Vega and Grundy, 1990c). Therefore, if fibrates are employed it is usually necessary to combine them with a statin to attain the non-HDL-cholesterol goal (East et al., 1988). Supplements of long chain n-3 polyunsaturated fatty acids present in fish oil, particularly eicosapentaenoic acid at doses of 3 g per day, have been shown to reduce plasma

triglycerides by up to 30 percent, and at higher doses (9 g per day) by up to 50 percent (Harris et al., 1990; Connor 1999). They represent an alternative for use in combination with statins.

Rarely, persons with high triglycerides have familial dysbetalipoproteinemia. In this condition, excess triglycerides are transported in cholesterol-enriched VLDL remnants (beta-VLDL). The same therapeutic approaches are effective as in those with other genetic forms of high triglycerides. Weight reduction is effective in lowering beta-VLDL in overweight/obese persons. Fibrates and nicotinic acid are particularly efficacious for reducing beta-VLDL (Hoogwerf et al., 1984; Guyton 1999), but statins also can be effective (East 1986).

Very high triglycerides (≥500 mg/dL). When triglycerides are very high (≥500 mg/dL), drugs that raise triglycerides should be identified and preferably discontinued. Alcohol should be eliminated. If hyperglycemia is present, insulin or oral hypoglycemic drugs may be started or increased in dosage. When triglyceride levels are >1000 mg/dL, very low-fat diets (<15 percent of total calories as fat) should be started immediately to lessen chylomicronemia that contributes importantly to very high triglycerides. Weight reduction and increased physical activity as components of TLC should be emphasized. Triglyceride-lowering drugs (fibrates or nicotinic acid) are usually required and are efficacious in persons with very high triglycerides and often can prevent acute pancreatitis. Fibrates generally are the most practical choice (Garg and Grundy, 1989). Gemfibrozil (600 mg twice daily) has been reported to reduce serum triglycerides by a mean of 74 percent in persons with severe hypertriglyceridemia (Leaf et al., 1989) and eliminate chylomicrons from plasma. Fenofibrate appears to be similarly effective in persons with severe hypertriglyceridemia (Goldberg et al., 1989). The n-3 fatty acids likewise can lower triglycerides and may be used as adjunctive therapy (Harris et al., 1990; Connor 1999). Nicotinic acid also is effective, but high doses (>2 g/day) generally should be used cautiously in persons with elevated serum glucose; in these persons, nicotinic acid may worsen hyperglycemia. If the latter occurs, triglyceride levels may actually rise. For most persons with extremely high triglycerides, therapy can be considered successful if it reduces serum triglycerides to <500 mg/dL; often it is not possible to normalize triglycerides in these persons. The first priority for persons with severe hypertriglyceridemia is to prevent acute pancreatitis; a secondary goal is to reduce risk for CHD.

In very rare circumstances, triglyceride and chylomicron levels are extremely elevated from birth. Affected persons usually have a genetic form of complete absence of either lipoprotein lipase or apo CII, an activator of lipoprotein lipase (Santamarina-Fojo 1998). These persons run a high risk for pancreatitis throughout life. They are unresponsive to triglyceride-lowering drugs. Treatment consists of very low-fat diets, although the diet can be supplemented with medium-chain triglyceride, which does not form chylomicrons when absorbed.

3. Low HDL cholesterol (without hypertriglyceridemia)

a. Definition, causes and relationship to CHD

A low level of HDL cholesterol is associated with increased risk for CHD and is classified as a major risk factor for CHD. ATP III sets HDL-cholesterol level of <40 mg/dL as a categorical risk factor and designates it a factor that modifies the LDL goal. The causes of low HDL-

cholesterol levels and postulated mechanisms for its relationship to CHD are presented in Table VII.3–1.

Table VII.3–1. Low Serum HDL Cholesterol: Causes and Associations with CHD

Causes of Low HDL	Postulated Factors Associating Low HDL with CHD
Elevated serum triglycerides Overweight and obesity* Physical inactivity* Cigarette smoking Very high carbohydrate intake (>60% of total energy) Type 2 diabetes* Certain drugs† Genetic factors*	• Direct atherogenic effect of low HDL Postulated mechanisms: – Decreased reverse cholesterol transport – Increased LDL oxidation – Increased LDL aggregation – Increased arterial inflammation • Marker for atherogenic dyslipidemia ("lipid triad"): – Higher VLDL triglycerides and remnant lipoproteins – Small, dense LDL – Low HDL cholesterol • Marker for metabolic syndrome – Abdominal obesity – Atherogenic dyslipidemia – Elevated blood pressure – Insulin resistance and elevated plasma glucose – Prothrombotic state – Proinflammatory state • Cigarette smoking – Smoking lowers HDL cholesterol

* Overweight, obesity, physical inactivity, type 2 diabetes, and certain genetic factors may exert their effects on HDL-cholesterol levels in part through insulin resistance and commonly through higher triglyceride levels.

† Drugs include beta-blockers, anabolic steroids, progestational agents.

The causes of low HDL cholesterol also were presented in Section II.3. When serum triglycerides become borderline high (150–199 mg/dL), HDL-cholesterol levels begin to fall. When triglyceride levels are greater than 150 mg/dL, HDL-cholesterol concentrations frequently are <40 mg/dL in men (or <50 mg/dL in women) (Albrink et al., 1980; Phillips et al., 1981). Thus, the term *isolated low HDL* can be reserved for HDL-cholesterol levels <40 mg/dL in the presence of serum triglycerides <150 mg/dL. Causes other than elevated triglycerides listed in Table VII.3–1 account for most cases of isolated low HDL. In the United States, population, obesity and physical inactivity are major factors; genetic factors undoubtedly play an important role as well in many persons (Cohen et al., 1994). In rare cases, genetic defects in metabolism of HDL alone can cause isolated low HDL.

The relationship between HDL and CHD risk is complex (see Table VII.3–1). First, a low HDL per se may directly promote the development of coronary atherosclerosis and predispose to CHD. Several mechanisms have been implicated: impaired reverse cholesterol transport, loss of protection against atherogenicity of LDL, and reduction in HDL-carried, anti-atherogenic factors (Rubin et al., 1991; Plump et al., 1994; Tangirala et al., 1999; Tall 1998; van Lenten et al., 1995; Navab et al., 2000a,b). Some persons with severe deficiency of HDL do not manifest premature CHD (Romling et al., 1994; Takata et al., 1995); this suggests that HDL is not uniquely involved in atherogenesis, as is LDL. But this finding does not rule out the possibility that HDL provides some protection against development of CHD. Second, a low HDL commonly is a *marker* for

atherogenic dyslipidemia (lipid triad)—raised triglycerides and remnant lipoproteins, small LDL particles, and low HDL (Schaefer et al., 1994; Phillips et al., 1981). Both remnants and small LDL may have independent atherogenic properties (see Section II.3). Finally, a low HDL cholesterol can be a *marker* for the metabolic syndrome; many persons with isolated low HDL have the other risk factors characteristic of this syndrome (Vega and Grundy, 1996). Besides atherogenic dyslipidemia, these persons often have hypertension and insulin resistance, the latter being indicated by the presence of abdominal obesity. Prothrombotic and proinflammatory states typically are noted in persons with the metabolic syndrome (see Section II.6). Finally, cigarette smoking reduces HDL-cholesterol concentrations and represents another factor contributing to the HDL-CHD relationship in smokers.

b. Therapeutic considerations in persons with low HDL cholesterol

1) Clinical trial evidence

Several clinical trials suggest that raising HDL-cholesterol levels contributes to decreased risk for CHD (see Section II.3.c). Nonetheless, in these trials, changes in other lipoproteins also have occurred. For this reason, the benefit of raising HDL per se is not known with certainty. Several clinical trials have recruited persons with low HDL-cholesterol levels and no significant elevations of triglycerides (Table VII.3–2). These trials thus provide information on the benefit of lipoprotein modification in persons with low HDL-cholesterol levels. For example, the AFCAPS/TexCAPS (Downs et al., 1998) trial recruited men and women without cardiovascular disease who had relatively low HDL levels; in this study, LDL lowering with lovastatin reduced risk for CHD. Similar results were observed in persons with CHD treated with statins (see Table II.2–3). Furthermore, angiographic trials have documented reductions in progression of atherosclerosis in persons with low levels of HDL cholesterol treated with fluvastatin in the Lipoprotein and Coronary Atherosclerosis Study (LCAS) (Herd et al., 1997) or with lovastatin in the Post-Coronary Artery Bypass Graft Trial (The Post Coronary Artery Bypass Graft Trial Investigators 1997). In the latter trial, LDL-cholesterol levels were reduced moderately and markedly in two arms of therapy. For those subjects with low HDL-cholesterol levels, there was a marked reduction in risk in the group with LDL-cholesterol levels of 95 mg/dL as compared to 135 mg/dL. Finally, meta-analyses of statin trials showed no difference in benefit of LDL lowering between high HDL and low HDL strata (Table II.2–3). These studies taken together document that lowering LDL cholesterol in persons with isolated low HDL significantly reduces risk for CHD.

The VA-HIT study (Rubins et al., 1999) specifically targeted persons with isolated low HDL for gemfibrozil therapy. Persons in this trial had low levels of HDL cholesterol (mean 32 mg/dL), only modestly elevated triglycerides (mean 161 mg/dL), and LDL-cholesterol concentrations <140 mg/dL (mean 111 mg/dL). The reduction in major cardiovascular events in this trial observed with gemfibrozil therapy was attributed in part to raising HDL-cholesterol levels. Likewise, the decrease in major coronary events during gemfibrozil therapy in the Helsinki Heart Study (Frick et al., 1987) was estimated to be due partly to an increase in HDL-cholesterol levels.

Table VII.3–2. Low HDL-C: Clinical Trial Evidence and HDL Response to Therapy

Clinical Trial Evidence of Benefit of Therapy for Persons with Low HDL	Aggregate Evidence from Literature Review on HDL Response to Therapy
• Statin trials: LDL-lowering therapy reduces CHD risk in persons with low HDL – 4S – CARE – LIPID – WOSCOPS – AFCAPS/TexCAPS – LCAS – Post CABG • Nicotinic acid trial: – Nicotinic acid effectively raises HDL – Coronary Drug Project indicated that nicotinic acid reduces major coronary events • Fibric acid trials: – Fibrates favorably modify atherogenic dyslipidemia – Multiple fibrate trials in aggregate produce favorable trend for reduction of CHD events (see Section II.3)	• Weight reduction – 5–20% increase in HDL • Physical activity – 5–30% increase in HDL • Smoking cessation – 5% increase in HDL • Statin therapy – 5–10% increase in HDL • Fibrate therapy – 5–15% increase in HDL • Nicotinic acid therapy – 15–30% increase in HDL

2) Recommendations for low HDL cholesterol in persons with CHD or CHD risk equivalents, 10-year risk >20 percent

Low HDL-cholesterol levels are common in persons with CHD or CHD risk equivalents. In these persons, the primary target of therapy is LDL cholesterol. If the person with low HDL cholesterol has the metabolic syndrome, TLC should emphasize weight reduction and increased physical activity. Consideration can also be given to using a drug to modify HDL metabolism. For example, the VA-HIT trial evaluated the effects of gemfibrozil therapy in CHD patients with low HDL; the significant reduction of major coronary events observed in this trial supports the efficacy of this approach. Nicotinic acid can be used instead of a fibrate; it has the advantage of raising HDL cholesterol two- to three-fold more than fibrates. Finally, the combined use of an LDL-lowering drug with either a fibrate or nicotinic acid is attractive for high risk persons with isolated low HDL to improve the whole lipoprotein profile. Using drugs in combination may increase the likelihood of side effects.

3) Considerations for persons with low HDL cholesterol in other risk categories, 10-year risk ≤20 percent

In persons *without* CHD or CHD risk equivalents, low HDL cholesterol counts as a risk factor that modifies the goal for LDL cholesterol. The first line of therapy for isolated low HDL is to

maximize life habit changes. These include all components of TLC—reduction in cholesterol-raising nutrients, LDL-lowering options, weight reduction, and increased physical activity. The AFCAPS/TexCAPS trial demonstrated that LDL lowering in persons with low HDL to reduces CHD risk. Whether a drug to modify atherogenic dyslipidemia, i.e., fibrate or nicotinic acid, could achieve similar benefit in primary prevention is uncertain because primary prevention trials with these drugs have not targeted persons with isolated low HDL.

Persons with low HDL cholesterol and 0–1 other risk factor can present a quandary for clinical management. Apparently some forms of low HDL are atherogenic, whereas others are not. Some authorities advocate the use of emerging risk factors to assist in risk assessment in apparently low risk persons with low HDL. For example, noninvasive assessment of coronary or carotid atherosclerosis by coronary EBCT or carotid sonography, respectively, could assist in identifying which "low-risk" persons with low HDL-cholesterol levels are at higher risk.

4. Diabetic dyslipidemia

a. Definition of diabetic dyslipidemia

The term *diabetic dyslipidemia* essentially refers to *atherogenic dyslipidemia* occurring in persons with type 2 diabetes (Durrington 1999). It is characterized by elevated TGRLP, small LDL particles, and low HDL-cholesterol concentrations. Diabetic dyslipidemia must be considered as one component of the metabolic syndrome, which is exceedingly common in persons with type 2 diabetes.

b. Role of elevated LDL and other risk factors in causation of CHD in persons with diabetes (Table VII.4–1)

Table VII.4–1. Role of CHD Risk Factors in Persons with Diabetes: Evidence and Postulated Mechanisms of Causation

Risk Factor	Evidence and Mechanisms
LDL cholesterol	• Borderline high LDL cholesterol (130–159 mg/dL) common in persons with diabetes • High LDL cholesterol (≥160 mg/dL) occurs at average rates in persons with diabetes • Statin trials show benefit from LDL-lowering therapy • 4S trial: Simvastatin therapy reduced CHD events in persons with diabetes by 53% • CARE/LIPID pooled data: pravastatin therapy significantly reduced CHD events in persons with diabetes
Atherogenic dyslipidemia	• High triglycerides, low HDL, and small LDL common in type 2 diabetes • Elevated triglycerides appear to be an "independent" risk factor in persons with diabetes
Hyperglycemia	• Hyperglycemia is an independent risk factor for CHD • Several mechanisms postulated – Glycation of arterial wall proteins – Atherogenic advanced glycation end-products (AGEs) – Induction of a proinflammatory state • Treatment of hyperglycemia reduces microvascular complications in both type 1 diabetes and type 2 diabetes • Treatment of hyperglycemia may reduce macrovascular complications (DCCT) (Diabetes Control and Complications Trial Research Group 1993) • Ongoing clinical trials are underway to further test efficacy for glycemic control on macrovascular clinical events
Hypertension	• Increased frequency of hypertension in persons with diabetes • Commonly associated with insulin resistance • Diabetic renal disease may be a factor • Hypertension major cause of morbidity in persons with diabetes • Treatment of hypertension reduces cardiovascular morbidity in persons with diabetes (UKPDS) (UK Prospective Diabetes Study 1998d)
Cigarette smoking	• Cigarette smoking compounds the risk for CHD accompanying diabetes
Gender considerations	• The protective effect of female sex against CHD is reduced in persons with diabetes • Therefore, treatment guidelines are the same for men and women with diabetes
Prothrombotic state	• Persons with diabetes have higher levels of prothrombotic factors than nondiabetic persons; these may contribute to higher risk for CHD in persons with diabetes
Proinflammatory state	• Persons with diabetes have higher levels of proinflammatory factors than nondiabetic persons; these may reflect increased risk for major coronary events in persons with diabetes

LDL-cholesterol levels in persons with diabetes typically are not higher than those of persons without diabetes who are matched for age, sex, and body weight (Strandberg et al., 1996; Sosenko et al., 1993; Barrett-Connor et al., 1987). Nonetheless, since LDL levels are relatively high in populations such as the United States, it is invalid to conclude that elevated LDL cholesterol is not a significant "risk factor" in persons with type 2 diabetes (Barrett-Connor et al., 1987). Moreover, the number of LDL particles in persons with type 2 diabetes usually is greater than is reflected by LDL-cholesterol levels because LDL particles are small and partially depleted of cholesterol (Haffner et al., 1994). Moreover, the adverse atherogenic interaction between elevated LDL and other risk factors of the metabolic syndrome imparts greater pathological significance to LDL cholesterol in type 2 diabetes.

The importance of LDL cholesterol in type 2 diabetes is confirmed by reports from major clinical trials of statin therapy. The 4S, CARE, and LIPID trials (Scandinavian . . . Study Group 1994; Sacks 2000a; Long Term Intervention . . . Study Group 1998) each contained subgroups of persons with diabetes. Subgroup analysis of each of these trials revealed a strong trend towards reduction in major coronary events with LDL lowering in persons with diabetes. In the 4S trial (Pyorala et al., 1997; Haffner et al., 1999a) and CARE study (Goldberg 1998), reductions in major coronary events in subgroups with diabetes were statistically significant. In the LIPID trial the apparent reduction in risk in persons with diabetes, although not statistically significant, was consistent with the benefit found in other subgroups. In a more recent pooled analysis of pravastatin studies (CARE + LIPID), patients with diabetes had a significantly reduced risk for CHD on drug therapy (Long Term Intervention . . . Study Group 1998, Sacks et al., 2000b). Thus, the combined results of three major clinical trials strongly suggest that LDL-lowering therapy in CHD patients with type 2 diabetes reduces risk for CHD similarly to that observed in persons without diabetes (see Table II.12–4). Unfortunately, few clinical trial data are available on the efficacy of LDL lowering in diabetic persons without CHD (primary prevention). Nonetheless, on the basis of secondary prevention trials, the ATP III panel concludes that LDL cholesterol is the primary lipid target in persons with diabetes.

Persons with diabetes often have other abnormalities in serum lipids and lipoproteins that may contribute to the increased risk for CHD accompanying diabetes. The term *diabetic dyslipidemia* is synonymous with *atherogenic dyslipidemia* (Verges 1999; Durrington 1999; Kreisberg 1998). It must be recognized, nonetheless, that abnormalities in lipids and lipoproteins represent only one factor among several that are responsible for the increased risk in persons with diabetes. Other factors include hypertension, hyperglycemia, insulin resistance, excessive glycation of cellular proteins, increased amounts of advanced glycation end products (AGEs), increases in proinflammatory and prothrombotic factors, and cigarette smoking. The importance of controlling nonlipid risk factors is emphasized by controlled clinical trials. The UKPDS showed that treatment of hypertension improved cardiovascular outcome in persons with type 2 diabetes (UK Prospective Diabetes Study Group 1998c,d). In addition, the DCCT (Diabetes Control and Complications Trial Research Group 1993) found that improved glycemic control in persons with type 1 diabetes significantly reduced microvascular complications with a trend towards reduction in macrovascular events including myocardial infarction. Thus, maximal reduction in cardiovascular risk in persons with diabetes requires a multifactorial approach in which all of the major risk factors are treated.

c. Therapeutic recommendations for lipoprotein disorders in persons with diabetes

1) Special therapeutic considerations according to LDL-cholesterol level (Table VII.4–2)

Table VII.4–2. Special Considerations for Lipid Management in Persons with Diabetes

Serum LDL-Cholesterol Level	Special Therapeutic Considerations
LDL ≥130 mg/dL	• Initiate TLC in all persons • Many persons, both type 1 and type 2 diabetes, will require LDL-lowering drugs (statins usually first choice) • LDL goal: <100 mg/dL • If triglycerides ≥200 mg/dL, non-HDL-C goal: <130 mg/dL • If LDL ≥130 mg/dL, LDL-lowering drug usually indicated along with TLC • Type 1 diabetes: clinical judgment required for how intensively to employ LDL-lowering therapy to reach an LDL of <100 mg/dL (however, consider LDL-lowering drug if LDL ≥130 mg/dL) • Type 2 diabetes: generally delay management of atherogenic dyslipidemia until LDL goal has been achieved • If triglycerides ≥200 mg/dL, consider treatment with fibrate or nicotinic acid (either as alternative to or in combination with LDL-lowering drug) to achieve goal for non-HDL • Intensively treat nonlipid risk factors (hypertension, cigarette smoking, hyperglycemia) • If nicotinic acid is employed, use relatively low doses (<3 g/day)
Baseline LDL 100–129 mg/dL	• Initiate TLC in all persons • Intensively treat nonlipid risk factors • Consider therapeutic options: intensive TLC; LDL-lowering drug; drug to lower triglycerides or raise HDL; control of nonlipid risk factors • If triglycerides ≥200 mg/dL, non-HDL goal: <130 mg/dL • If triglycerides ≥200 mg/dL, consider treatment with fibrate or nicotinic acid (either as alternative to or in combination with LDL-lowering drug) to achieve goal for non-HDL • If nicotinic acid is employed, use relatively low doses (<3 g/day)

Table VII.4–2. (continued)

Serum LDL-Cholesterol Level	Special Therapeutic Considerations
On-Treatment LDL 100–129 mg/dL	• Intensify TLC in all persons • Intensively treat nonlipid risk factors • If triglycerides <200 mg/dL, consider intensifying LDL-lowering therapy (e.g., higher dose of statin or combining a statin with a bile acid sequestrant) • If triglycerides ≥200 mg/dL, consider adding fibrate or nicotinic acid to statin therapy to achieve non-HDL-C goal <130 mg/dL* • If nicotinic acid is employed, use relatively low doses (<3 g/day)
Baseline LDL <100 mg/dL	• Initiate TLC in all persons to reduce overall risk • Intensively treat nonlipid risk factors • If triglycerides ≥200 mg/dL, consider using a fibrate or low-dose nicotinic acid to achieve non-HDL-C goal <130 mg/dL. • If nicotinic acid is employed, use relatively low doses (<3 g/day)

* The combination of statins plus fibrates is accompanied by increased risk for myopathy. Persons should be instructed to be aware of the signs and symptoms of myopathy and to report these immediately to the physician.

Since diabetes falls into the category of CHD risk equivalent, the goal for LDL cholesterol in persons with diabetes, particularly type 2 diabetes, is <100 mg/dL. The rationale for identifying diabetes as a CHD risk equivalent was given in Section II. Nonetheless clinical experience and judgment are required for the management of lipids when persons have diabetes. There is widespread agreement that LDL cholesterol should be reduced to less than 130 mg/dL in almost all persons with diabetes, and the American Diabetes Association recommends an LDL-cholesterol goal of less than 100 mg/dL in most diabetic persons (American Diabetes Association 2001).

TLC should be started in all persons when LDL cholesterol is ≥130 mg/dL. Most persons with diabetes will require an LDL-lowering drug to reach the LDL goal of <100 mg/dL. If the patient also has high triglycerides (≥200 mg/dL), non-HDL cholesterol will be a secondary target. Simultaneous control of other risk factors is essential.

When baseline LDL-cholesterol levels are in the range of 100–129 mg/dL, several therapeutic options are available. First, maximal changes in life habits, including reduction of saturated fat and cholesterol intakes, use of LDL-lowering dietary options (plant stanol/sterols and increased viscous fiber), weight reduction, and increased physical activity may achieve an LDL-cholesterol level <100 mg/dL in some persons without the need for LDL-lowering drugs. Second, in those who do not achieve an LDL cholesterol <100 mg/dL with TLC alone, an LDL-lowering drug can be added to the regimen. Alternatively, a drug (i.e., fibrate) that primarily targets atherogenic dyslipidemia can be used. Without question, maximal control of nonlipid risk factors, e.g., hyperglycemia and hypertension, is necessary in persons with low LDL levels. In persons with type 2 diabetes in whom LDL-cholesterol levels have been reduced into the range of 100–

129 mg/dL on LDL-lowering drugs, clinical judgment is required to determine whether or how to intensify therapy. One option is to increase the dose of the LDL-lowering drugs to further reduce LDL-cholesterol levels to <100 mg/dL; along this line, two LDL-lowering drugs (e.g., statin + bile acid sequestrant) can be combined. Alternatively, intensification of LDL-lowering therapy with TLC may sufficiently lower LDL levels without changing drug therapy. Finally, a fibrate can be added to an LDL-lowering drug to improve atherogenic dyslipidemia. The advantage of combining a fibrate with an LDL-lowering drug is that the overall lipoprotein pattern is improved. The disadvantage is that it increases the risk for severe myopathy.

For LDL lowering, statins are usually the drugs of choice in persons with diabetic dyslipidemia. They are highly efficacious for LDL reduction, and they are well tolerated by persons with diabetes. hoc analysis of major clinical trials shows that statins reduce risk for major coronary events in persons with diabetes. Moreover, statins lower VLDL remnants as well as LDL, and often can achieve the secondary goal for non-HDL cholesterol in hypertriglyceridemic persons with diabetes. Bile acid sequestrants also can be used for LDL lowering in persons with diabetes (Garg and Grundy, 1994). However, they do not reduce VLDL cholesterol, and in some persons, actually raise triglyceride levels.

When baseline LDL cholesterol is <100 mg/dL, the non-HDL cholesterol should be estimated to determine whether it is still a target for cholesterol-lowering therapy. TLC is indicated for treatment of atherogenic dyslipidemia and the metabolic syndrome. Other risk factors should be controlled. If the triglyceride level is ≥200 mg/dL, use of a fibrate or a low dose of nicotinic acid (<3 g/day) may assist in achieving the non-HDL-cholesterol goal of <130 mg/dL (Garg and Grundy, 1990).

2) Comments on specific drug classes used in management of lipid disorders in persons with diabetes

Statins are first-line therapy for reducing LDL-cholesterol levels in persons with diabetes and they are generally well tolerated. They have the advantage of lowering VLDL cholesterol as well as LDL cholesterol; thus they can assist in attaining the non-HDL-cholesterol goal when triglyceride levels are ≥200 mg/dL. Bile acid sequestrants also are effective LDL-lowering drugs in persons with diabetes (Garg and Grundy, 1994). Their potential utility for LDL lowering either as monotherapy or in combination with statins should not be overlooked. They generally are not contraindicated simply because of their tendency to raise triglycerides. Nonetheless, triglyceride levels should be monitored.

Fibrates favorably modify diabetic dyslipidemia. They are well tolerated, and do not worsen hyperglycemia. They probably produce some reduction in CHD risk, and could be used in persons who have low LDL-cholesterol levels and atherogenic dyslipidemia (Rubins et al., 1999). In addition, they can be combined with statins to improve the overall lipoprotein pattern (Garg and Grundy, 1989). For many years, fibrates were considered first-line therapy for persons with diabetes. However, the results of recent clinical trials now favor use of statins before fibrates in most persons. Still, the combination of statin + fibrate is attractive in persons with diabetes who have atherogenic dyslipidemia but in whom LDL lowering is required to achieve

the LDL-cholesterol goal. Clinical trials are currently underway to test the efficacy of statin + fibrate in treatment of diabetic dyslipidemia.

Nicotinic acid also has a favorable effect on diabetic dyslipidemia. Recent clinical trials (Elam et al., 2000; Grundy et al., 2001b) in persons with diabetes indicated that low doses of nicotinic acid are accompanied by only modest deterioration in glucose control with no changes in HbA1C levels. Unfortunately, nicotinic acid therapy can increase insulin resistance (Kahn et al., 1989; Kelly et al., 2000) and clinical experience has shown that in rare instances, diabetic dyslipidemia is worsened with nicotinic acid therapy.

Treatment with hypoglycemic agents also can improve diabetic dyslipidemia. Insulin therapy, sulfonyl ureas, metformin, and glitazones can all lower triglyceride levels. Although they may not be as effective as fibrates in modifying atherogenic dyslipidemia, control of hyperglycemia should be maximized before considering a fibrate in combined lipid-lowering drug therapy. If hypertriglyceridemia can be adequately controlled by glucose-lowering therapy, a lipid-lowering drug may not be needed.

5. Other secondary dyslipidemias

Hypothyroidism. A low level of thyroid hormone raises LDL-cholesterol levels. The importance of this condition is that some persons have "masked" or subclinical hypothyroidism. For this reason, any patient with LDL cholesterol >160 mg/dL should be tested for hypothyroidism.

Nephrotic syndrome. This condition is characterized by proteinuria, edema, and severe hyperlipoproteinemia. Elevation of LDL cholesterol is the major lipid abnormality, whereas hypertriglyceridemia develops in some persons. There is evidence that nephrotic dyslipidemia increases risk for CHD (Alexander et al., 1974; Berlyne and Mallick, 1969; Mallick and Short, 1981). Therefore, if hyperlipidemia persists despite specific treatment for renal disease, consideration can be given to use of cholesterol-lowering drugs. Although several lipid-lowering agents appear to modify elevated lipid levels, statins are particularly effective (Grundy 1990; Rabelink 1988; Matzkies et al., 1999; Toto et al., 2000).

Other renal disorders. Various dyslipidemias have been reported in persons with chronic renal failure, in those on hemodialysis, and in persons following transplantation (Attman et al., 1987). Hypertriglyceridemia and low HDL-cholesterol levels are the most frequently described lipid abnormalities with chronic renal failure and hemodialysis (Bagdade et al., 1968; Rader and Rosas, 2000). Hypercholesterolemia and hypertriglyceridemia often occur in persons following renal transplantation (Casaretto et al., 1974; Gokal et al., 1979). Although persons with these conditions have been reported to be predisposed to CHD, they often have other risk factors (e.g., hypertension, smoking, and diabetes) that deserve primary attention. Few studies have been carried out on treatment of dyslipidemia in these conditions, and a cautious approach should be taken since these persons are prone to drug side effects. For example, they are at increased risk for severe myopathy from both fibrates and statins.

Obstructive liver disease. Biliary obstruction can lead to severe hypercholesterolemia that is resistant to conventional cholesterol-lowering drugs. The only effective therapy is treatment of the underlying liver or biliary tract disease.

Protease-inhibitor induced dyslipidemia. Although protease inhibitors have improved morbidity and mortality in patients with human immunodeficiency virus (HIV), these drugs unfortunately can cause serious metabolic disorders (Hruz et al., 2001; Penzak and Chuck, 2000; Graham 2000). The latter include peripheral lipodystrophy, increased visceral fat, hyperlipidemia, insulin resistance, and diabetes. The lipid pattern typically is that of atherogenic dyslipidemia (elevated triglyceride and low HDL-cholesterol levels). The mechanisms underlying the metabolic complications are unknown, although they resemble those of a genetic disorder called familial partial lipodystrophy (Garg 2000). To date there is limited experience with lipid-lowering drugs for treatment of protease-inhibitor induced lipodystrophy. However, clinical experience indicates that both fibrates and statins will reduce serum triglycerides and cholesterol in this condition (Penzak and Chuck, 2000). Fibrates may be especially useful to prevent the occurrence of acute pancreatitis associated with severe hypertriglyceridemia.

6. Persons with high blood cholesterol and concomitant hypertension

In 1990, NHLBI published a report of a working group on management of patient with concomitant high blood cholesterol and hypertension (Working Group Report . . . High Blood Cholesterol 1990; Working Group . . . High Blood Cholesterol 1991). The major findings of this study are reviewed and updated in this section. Both high blood cholesterol and high blood pressure are common in U.S. adults, and these two conditions frequently coexist. Persons with high blood cholesterol have a higher than expected prevalence of hypertension, and persons with hypertension have a higher than expected prevalence of high blood cholesterol. According to unpublished data from NHANES II, 40 percent of the 51 million individuals with hypertension (blood pressure ≥140/90 mmHg or currently taking antihypertensive medications) have cholesterol levels ≥240 mg/dL, and 46 percent of those with cholesterol levels ≥240 mg/dL have hypertension. The risk gradient for blood pressure (systolic and diastolic) is similar to that for serum cholesterol; the higher the blood pressure, the greater the risk of CHD (Lerner and Kannel, 1986). In persons with both elevated cholesterol and high blood pressure, CHD risk is synergistically increased. Conversely, reducing blood pressure, like cholesterol lowering, decreases risk for cardiovascular disease (MacMahon et al., 1986).

a. Therapeutic considerations

In persons with concomitant hypertension and hypercholesterolemia, both conditions should be treated aggressively, especially in persons with known CHD. Diet and other lifestyle therapies are the essential first steps of therapy for elevations of both blood pressure and cholesterol. The principles of dietary therapy are similar in both cases and include reductions of calories, saturated fat, cholesterol, and alcohol consumption; sodium reduction and ample potassium intake are also important for control of hypertension. The recommended diet should emphasize fruits, vegetables, and low-fat dairy products (Obarzanek et al., 2001; Sacks et al., 2001). In overweight persons, weight reduction is very important and essential to the management of elevated blood pressure (Reisin et al., 1983) as well as for high blood cholesterol. Persons should

be reminded that weight reduction and control is a chronic rather than an acute treatment and that successful weight control will be achieved only through long-term lifestyle modification that emphasizes both nutritional balance and physical activity (Eckel 1997; National Institutes of Health 1998a,b). Exercise is also important because of its benefits on cardiovascular fitness and weight reduction as well as lowering of blood pressure and cholesterol (U.S. Department of Health and Human Services 1996b). Smoking cessation should also be included in the life habit changes required to improve cholesterol and blood pressure levels.

b. Effects of antihypertensive agents on serum lipids

Several antihypertensive agents affect serum lipid levels, whereas others do not (Weinberger 1985; Lardinors and Neuman, 1988). For example, calcium channel antagonists, angiotensin converting enzyme inhibitors, hydralazine, minoxidil, potassium-sparing diuretics, and reserpine have minimal if any effects on serum lipids. Higher doses of thiazide diuretics can cause modest and often transient elevations (5–10 mg/dL) in serum total and LDL cholesterol and serum triglycerides with little or no adverse effects on HDL cholesterol. The effects of loop diuretics are similar to those of thiazides with increases in total and LDL cholesterol, whereas HDL-cholesterol levels are generally lower in persons on furosemide. Data regarding indapamide are inconclusive, but suggest a neutral effect. Alpha-1-adrenergic blockers and centrally acting alpha-2-receptor agonists have a slight beneficial effect on blood lipids by decreasing total and LDL cholesterol. In general, beta-blockers without intrinsic sympathomimetic activity (ISA) or alpha-blocking properties tend to reduce HDL cholesterol, increase serum triglycerides, and have variable effects on total serum cholesterol. These effects are very modest and should not play a role in the selection of specific antihypertensive agents. Beta-blockers with ISA and the beta-blocker labetalol (which has alpha-1-adrenergic blocking properties) produce no appreciable changes in lipid levels.

The effects of antihypertensive drugs on the efficacy of lipid-lowering agents have not been carefully evaluated, but among participants in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), those who were taking thiazide diuretics did not reduce LDL cholesterol as much as those who were not using thiazide diuretics (Weinstein and Statson, 1977; Glueck et al., 1986). Regardless of the potential of thiazide diuretics to raise serum cholesterol levels, they are still considered to be first-line therapies for hypertension (JNC VI 1997; Joint National Committee . . . Pressure 1997). Moreover, lower doses of thiazides appear to have less of a cholesterol-raising action as well as few other side effects (Ames 1996; Freis 1995). For these reasons, use of lower doses of thiazides need not be excluded in antihypertension regimens in persons undergoing clinical cholesterol management.

c. Selection of antihypertensive therapy

When lifestyle measures alone do not achieve desired goals, the addition of drug therapy may be required. Selection of drug therapy requires consideration of benefits, effects of therapy on quality of life, concomitant diseases, and costs. In general, selection of specific antihypertensive drugs for persons with elevated LDL-cholesterol levels should follow the guidelines outlined in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI 1997; Joint National Committee 1997). Selection of

lipid-lowering agents in persons with elevated blood pressure should follow the guidelines listed elsewhere in this report.

Drug therapy for uncomplicated hypertension should begin with a diuretic or beta-blocker. In older patients, a diuretic is preferred and a DHP calcium antagonist can be considered. In certain comorbidities (such as CAD, heart failure, renal disease, diabetes), angiotensin converting enzyme inhibitors or calcium antagonists have special indications. Alpha blockers should not be used as monotherapy or in those at risk for developing heart failure (ALLHAT Officers and Coordinators . . . 2000). Diuretics may slightly raise LDL-cholesterol levels and some beta-blockers may depress HDL-cholesterol levels, but these drugs should not be avoided if their non-use means less than optimal blood pressure control; further, their possible adverse effects on lipids should be balanced by considerations of efficacy, tolerability, cost, and adherence. Some persons will have strong indications for one of these medications (for example, beta-blockers in the post-myocardial infarction patient and diuretics in persons with salt-dependent hypertension). Therefore, they are not contraindicated even in the presence of the dyslipidemia. Some persons are not sensitive to the adverse effects of diuretics on lipids, and in others a low-saturated-fat, low-cholesterol diet will blunt or negate these effects. It should be noted that in the Systolic Hypertension in the Elderly Program (SHEP Cooperative Research Group 1991), use of low doses of thiazides and/or beta-blockers reduced both stroke and CHD in older persons and in fact had limited adverse effects on lipids (Savage et al., 1998). Thus any adverse effect on plasma lipids in this trial did not offset their net beneficial effect.

d. Selection of lipid-lowering therapy

Selection of drug therapy for persons with elevated cholesterol is discussed in depth elsewhere in this document. Several potential adverse effects on blood pressure control may occur and should be kept in mind. Bile acid sequestrants may decrease absorption of thiazide diuretics and propranolol, and medications should be given 1 hour before or 4 hours after the bile acid sequestrant. Nicotinic acid may enhance the fall in blood pressure due to antihypertensive vasodilators. Fibric acids are more likely to produce myopathy in persons with renal failure; therefore, dosage should be decreased and persons carefully monitored. The FDA lists no specific drug interactions between statins and antihypertensive agents; however, patients with some forms of renal disease may be at increased risk for myopathy with statin therapy (Weise and Possidente, 2000; Stirling and Isles, 2001; Al Shohaib 2000).

e. Compliance with therapy

Although the risks of elevated blood pressure and cholesterol levels are well-known, and the benefits of treatment well established, many persons are not adequately controlled. In the case of hypertension, more than half of persons are either untreated or inadequately treated. Poor adherence to therapy is a major reason for inadequate control of high blood pressure. Approximately 50 percent of persons with hypertension fail to keep followup appointments, and only 60 percent take their medications as prescribed. Efforts aimed at improving control of hypertension and hypercholesterolemia must address barriers to effective adherence. These include poor doctor-patient communication, cost of therapy, and side effects of medications. Lack of attention (complacency) to achieving treatment goals by health care providers is another

important reason for inadequate control rates of hypertension (Berlowitz 1998). Physicians and patients must be mutually committed to the goals of therapy and achieving control of the risk factor. Physicians must communicate instructions clearly and prescribe therapies that are effective, affordable, and have minimal or no adverse effects on the patient's quality of life or overall cardiac risk profile. Persons must follow recommendations and alert their physicians to any problems with their medications—particularly those relating to side effects and cost.